REMARKS

Applicants thank the Examiner for the consideration given the present application. Upon entry of the present amendments, cancellations, and additions, Claims 2, 4, 5, 9, 11, and 18 – 31 will be pending in the present application.

It is noted that a Power of Attorney, explicitly authorizing the undersigned to prosecute this application, is transmitted herewith.

While Applicants traverse the present restriction requirement, Applicants confirm the telephonic election of Group II as detailed by the Examiner in the Office Action dated December 31, 2001. As such, all claims presented herein are now directed to those structures bearing a substituted piperidine ring formed by substituents R^2 and R^3.

In compliance with the finalized restriction requirement, Applicants have cancelled Claims 1, 3, 6, 8, 10, 14, 16, and 17. Claim 7 has also been cancelled. For organizational purposes, Claim 12 has been canceled and re-introduced as new Claim 24. Claims 13 and 15 have been canceled and replaced with new claims directed to compositions and methods. All cancellations should be deemed without prejudice; Applicants intend to file a divisional application directed to the non-elected and cancelled subject matter.

In addition, Claims 2, 4, 5, 9, and 11 have each been amended in order to modify their respective dependencies (such as to depend upon a newly added claim rather than an cancelled claim). No new matter is introduced through the amendments herein.

In further compliance with the restriction requirement, Applicants have added new Claims 18 – 31 as presented herein. These claims are specifically directed to the subject matter of the Examiner's defined Group II and are fully supported by the present specification.

As has been suggested by the Examiner, the title of the present specification has been amended to be more descriptive. No new matter is presented through the amendment of the title herein.

The Examiner has rejected Claims 1 – 5, 7, 9, 11, 13, and 15 as being drawn to an improper Markush group. With respect to those rejected claims still pending herein, Applicants are unable to respond to the Examiner's rejection because the rejection is not understood. Applicants request that the Examiner further articulate any legal issues based on a "variable core." As for the Examiner's recognition that Claim 1 contains compounds drawn to the non-elected rings formed by R^2 and R^3, Applicants have herein amended all claims for compliance with the restriction requirement.

The Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 1 – 5, 7, 9, 11, 13, and 15 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that use of the term "about" with reference to indivisible terms is indefinite. It is noted that Claims 1, 3, 7, 13, and 15 have been cancelled herein, however, newly presented claims also utilize the term "about."

Applicants respectfully traverse this rejection. Applicants are unaware of any precedent which precludes the use of "about" in the cited instances. To the contrary, use of the term "about" to modify a quantitative description is commonplace throughout the chemical patent arts. Indeed, the Patent Office has routinely allowed and granted patents which contain claims utilizing the term "about" to modify a quantitative description, even where the quantitative description is an indivisible whole number. For example, Chatterjee, U.S. Patent No. 6,329,377, issued December 11, 2001 and Gangjee, U.S. Patent No. 6,221,872, issued April 24, 2001, both of which list Mukund J. Shah as the relevant Patent Office Examiner, utilize the term "about" to modify indivisible chemical chain lengths. The context of usage in these granted patents is no different relative to Applicants' current usage. Applicants respectfully request that the Examiner withdraw the present rejection based on use of the term "about" because the rejection is improper.

The Examiner has rejected Claims 1 – 5, 7, 9, 11, 13, and 15 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that use of the term "active compound" in Claim 1 is indefinite. Applicants have cancelled Claim 1 and replaced such claim with new Claim 18. Moreover, Claim 15 has also been cancelled and replaced with new method Claims 29 – 31. None of the newly presented claims, or their respective dependents, utilize this terminology. Applicants therefore request the withdrawal of the present rejection because the rejection is now moot.

The Examiner has also rejected Claims 1 – 5, 7, 9, 11, 13, and 15 based on use of the term "heteroatom," in connection with the definition set forth in the specification. Applicants have herein amended the specification to require that the term "heteroatom" means an atom selected from sulfur, phosphorous, nitrogen, and oxygen. Support for this requirement is found in the original specification, in the amended paragraph herein. All claims are affected by this amendment to the specification, including those claims utilizing a term which ultimately depends upon the definition of "heteroatom" (*e.g.*, heterogeneous group, heterocyclic group, heteroaromatic group). Applicants therefore request the withdrawal of the Examiner's rejection since the claims are indeed definite.

The Examiner has also rejected Claims 1 – 5, 7, 9, 11, 13, and 15 based on use of the term "substituted" to modify various moieties used in the claims (*e.g.*, substituted carbocyclic, substituted heterocyclic). Applicants traverse this rejection, as compounds bearing various substituents are commonplace in the art and will be readily understood. Moreover, Applicants have provided various examples of substituents, for example, halogens (page 4, line 1), heterocyclic groups (page 4, lines 13 – 19), heterogeneous groups (page 4, lines 20 – 28), hydrocarbon groups (page 4, line 29 through page 5, line 6), and various other substituents. Moreover, as the Examiner has recognized, each of the defined terms set forth in the present specification guides the artisan to particularly preferred substituents for the referenced defined term. Even further, as set forth in the descriptions of the various moieties of the present compounds, Applicants have again delineated certain preferred substituents. For example, at page 8 lines 1 – 11, the specification lists certain groups which are preferred as substituents on the ring structure formed by R^2 and R^3. Even further, various examples of illustrative substituents are set forth on pages 28 – 50 of the present specification. As such, in conformance with the legal standard, one of ordinary skill in art will understand usage of the term "substituents" or "substituted" as is presently utilized. Applicants therefore assert that the present rejection is improper and should be withdrawn.

The Examiner has further rejected Claim 4 as being indefinite with regard to usage of the term "substituted heterocyclic group" and whether this term refers to the heterocycle formed by linking R^2 and R^3. In conformance with the present restriction requirement, Applicants have herein amended Claim 4 to refer specifically to the substituted piperidyl formed by R^2 and R^3. Accordingly, Applicants assert that the Examiner's rejection is moot and should be withdrawn.

For all of the above reasons, Applicants respectfully request that the Examiner withdraw the rejections based on 35 U.S.C. § 112, second paragraph.

The Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 1 – 5, 7, 9, 11 – 13, and 15 based on use of the terms biohydrolyzable amides, esters, and imides. The Examiner states that these terms are unduly functional and that it is not proper to describe compounds by their principal biological activity when more precise descriptions are available.

Applicants traverse this rejection. Indeed, Applicants are unaware of any prohibition against functionally-described claim limitations. Moreover, one having ordinary skill in the art will readily comprehend the biohydrolyzable amides, esters, and imides (also commonly referred to in the art as "pro-drugs") of the claimed structures. For example, one of ordinary skill in the

art will readily know which amides, esters, and imides will be biohydrolyzable (*i.e.*, typically relatively short chain amides, esters, and imides as is commonly understood) and will have sufficient guidance in the art relative to the identification and synthesis of such biohydrolyzable amides, esters, and imides (if needed). Indeed, the synthesis of such "pro-drugs" would be straightforward to one of even less than ordinary skill in this art. See e.g., basic organic chemistry texts such as Greene *et al.*, Protecting Groups in Organic Synthesis, 2nd Ed., Wiley & Sons, Inc., 1991 (referenced in the present specification at page 5, lines 18 – 20) and Mackie *et al.*, Guidebook to Organic Synthesis, 2nd Ed., Wiley & Sons, Inc., 1991.

It is for all of these reasons that the recited biohydrolyzable esters, amides, and imides of the defined compounds are sufficiently enabled. Given the explicitly defined and claimed structures of the present invention, one of ordinarily skill could readily determine and derive such esters, amides, or imides which are "pro-drugs", or biohydrolyzable, as limited. Applicants therefore respectfully request that the Examiner withdraw the rejection of claims based on inclusion of biohydrolyzable esters, amides, and imides of the defined structures.

The Examiner has further rejected Claims 1 – 5, 7, 9, 11 – 13, and 15 based on enablement, stating that the specification is only enabling for compounds of Claim 1 wherein A is piperidine and $-R^4-C(R^1)_2-R^5-$ is 2-hydroxy-3-(5-qunolinyloxy)propyl. In support of this statement, the Examiner further states that "[c]ompounds made and tested represent the scope of Claim 12, not claim 1." Indeed, since the Examiner cannot be aware of which compounds Applicants have or have not "made and tested," the Examiner appears to have based the rejection upon Applicants' own disclosure of particularly preferred limitations, including those which have been most often exemplified in the specification.

This is an improper analysis; indeed, there is absolutely no requirement that a patent applicant can claim only what is "made," "tested," or even exemplified. In performing the analysis in this flawed manner, the Examiner has failed to consider the proper test for enablement as set forth in MPEP 2164.08 which provides two stages of inquiry: 1) to determine how broad the claim is with respect to the disclosure; and 2) to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

With respect to the first stage of inquiry, the broadest claim describing the present invention is no broader than any disclosure in the specification. Indeed, as set forth herein (both with respect to now cancelled Claim 1 and newly presented independent Claim 18), each of the claimed limitations, including all groups and moieties of the present compound, is fully supported and described by the present specification. Moreover, each and every limitation of the dependent

claims (which are now all ultimately dependent upon Claim 18) is also fully supported by the present specification.

With regard to the second stage of inquiry, Applicants have either disclosed specifications regarding how to make and use the compounds, compositions, and methods, or such specifications will be well known to one of ordinary skill in the art in view of Applicants' disclosure and/or public knowledge in the art. For example, Applicants dedicate approximately 22 pages of specification to methods of making the claimed compounds. Page 28 presents various texts for consultation, followed at pages 29 and 30 by a description of typical starting materials and reagents. At page 31, and progressing for approximately 19 pages more, Applicants provide detailed descriptions related to methods of making various side chains and core groups. To illustrate, and quite contrary to the Examiner's argument, Examples 8 – 27 demonstrate the synthesis of various $-R^4-C(R^1)_2-R^5-$ moieties which are not the 2-hydroxy-3-(5-qunolinyloxy)propyl chain cited by the Examiner.

Moreover, for those side chains and core groups not exemplified, the ordinarily skilled artisan will understand how to apply known and described principles to make other compounds within the scope of the claims. Indeed, the examples are merely illustrative of various ways in which the claimed compounds can be made – there is no statutory requirement for the disclosure of a specific example since a patent specification is not intended nor required to be a production specification. See MPEP 2165.02 (II) and *In re Gay*, 135 USPQ 311 (CCPA 1962).

With regard to the enablement requirement relating to "how to use," Applicants have further provided more than adequate description in this regard. For example, at pages 51 – 56, Applicants provide various assays which may be utilized to measure MDR activity and / or inhibition of transport protein activity, as well as various compositions (including oral and parenteral compositions) which may be formulated. Again, these examples are merely illustrative and are not meant to limit the invention as claimed.

For all of the above reasons, Applicants assert that each and every element of the claimed invention, including all embodiments, is fully enabled with respect to now cancelled Claim 1 and newly pending Claim 18. Applicants therefore respectfully request that the Examiner withdraw this rejection of the claims.

The Examiner has further rejected Claim 15 as being non-enabling with respect to inhibition of transport protein activity. Specifically, the Examiner states that the claim would read on inhibition in mammals having normal transport protein activity, mammals having below-normal transport protein activity, and those which are asymptomatic having upregulated transport protein activity. It is noted that Claim 15 is now cancelled herein and therefore this rejection is

moot. Moreover, new method Claims 29 – 31 are directed to methods selected from the group consisting of treating multidrug resistance, inhibiting transport protein activity, and combinations thereof, comprising administering to a mammal *in need of such treatment or inhibition* the composition. Accordingly, the methods read on administration to mammals needing inhibition of transport protein activity and are fully enabled.

The Rejection Under 35 U.S.C. §102(b) Based on Vicar, Balaspiri, or Kovacs

The Examiner has rejected Claims 1 – 3 and 7 under 35 U.S.C. §102(b) based on each of Vicar *et al., Collection Czechoslov. Chem. Commun.*, Vol. 37 (1972) (herein referred to as "Vicar"), Balaspiri et al., Acta Phys. Chem., Vol. 20 (1 – 2), pp. 105 – 110 (1974) (herein referred to as "Balaspiri"), and Kovacs, Pharmacol. Biochem. Behav., Vol 31(4), pp. 833 – 837 (1988) (herein referred to as "Kovacs"). The Examiner cites two specific compounds disclosed in Vicar, one disclosed in Balaspiri, and one disclosed in Kovacs, all of which contain 1-carbonyl benzyloxy moieties attached to a modified piperidine ring structure. In view of the present claim cancellations and additions, Applicants assert that each of these references fails to anticipate the presently claimed invention. Indeed, new independent Claim 18 (which has replaced Claim 1 in view of the restriction requirement), upon which all of the present claims depend, does not include carbonyl as among the selected moieties for R^4, but rather utilizes $-S(O)_2-$, -C(O)C(O)-, or $-CH(R^1)-$. As such, the presently pending claims are novel and patentable over each of Vicar, Balaspiri, and Kovacs, and the rejection should be withdrawn as moot.

The Rejection Under 35 U.S.C. §102(b) Based on Martin

The Examiner has rejected Claims 1 – 3 and 7 under 35 U.S.C. §102(b) based on Martin et al., "Enantioselective Protonation of Amide Enolates Derived from Piperidine-2-Carboxylic Acid," *Tetrahedron Letters*, Vol. 38, No. 41, pp. 7181 – 7182 (1997) (herein referred to as "Martin"). The Examiner cites one compound disclosed in Martin which contain a 1-carbonyl methoxy moiety attached to a modified piperidine ring structure. In view of the present claim cancellations and additions, Applicants assert that this reference fails to anticipate the presently claimed invention. Indeed, new independent Claim 18 (which has replaced Claim 1 in view of the restriction requirement), upon which all of the present claims depend, does not include carbonyl as among the selected moieties for R^4, but rather utilizes $-S(O)_2-$, -C(O)C(O)-, or $-CH(R^1)-$. As such, the presently pending claims are novel and patentable over Martin, and the rejection should be withdrawn as moot.

The Rejection Under 35 U.S.C. §102(a) Based on Guzi

The Examiner has rejected Claims 1 – 3 and 7 under 35 U.S.C. §102(a) based on Guzi *et al.*, WO 00/37458, published June 29, 2000 (herein referred to as "Guzi"). The Examiner cites compounds disclosed in Guzi which contain a 1-carbonyl alkoxy moiety attached to a modified piperidine ring structure. In view of the present claim cancellations and additions, Applicants assert that this reference fails to anticipate the presently claimed invention. Indeed, new independent Claim 18 (which has replaced Claim 1 in view of the restriction requirement), upon which all of the present claims depend, does not include carbonyl as among the selected moieties for R^4, but rather utilizes $-S(O)_2-$, $-C(O)C(O)-$, or $-CH(R^1)-$. Guzi, including the various examples and disclosure as a whole, fail to anticipate the presently pending claims. As such, Applicants' claims are novel and patentable over Guzi, and the rejection should be withdrawn as moot.

The Rejection Under 35 U.S.C. §102(b) Based on Xue

The Examiner has rejected Claims 1 – 3 and 7 under 35 U.S.C. §102(b) based on Xue *et al.*, WO 99/65867, published December 23, 1999 (herein referred to as "Xue"). The Examiner cites a specific compound described on page 108 of Xue (compound 75), wherein an ethyl moiety is attached to a modified piperidine ring structure. In view of the present claim cancellations and additions, Applicants assert that this reference fails to anticipate the presently claimed invention. Indeed, new independent Claim 18 (which has replaced Claim 1 in view of the restriction requirement), upon which all of the remaining claims depend, contains a proviso that wherein R^4 is $-CH(R^1)-$, and R^5 is $-O_rR^6-$, then r is 1. This proviso is fully supported by the present specification such as, for example, in Example 7 at page 34. Accordingly, the $-R^4-(C(R^1)(R^1))_r-R^5$ moiety of the present compounds cannot be an ethyl moiety. Xue, including the various examples and disclosure as a whole, fails to anticipate the presently pending claims. As such, Applicants' claims are novel and patentable over Xue, and the rejection should be withdrawn as moot.

The Rejection Under 35 U.S.C. §102(b) Based on Sato

The Examiner has rejected Claims 1 – 3, 11, 13, and 15 under 35 U.S.C. §102(b) based on Sato *et al.*, U.S. Patent 5,506,239, issued April 9, 1996 (herein referred to as "Sato"). The Examiner cites one compound from Sato, stating that this compound anticipates Applicants' claims. The compound contains an unsubstituted piperidine ring which forms an amide linkage with a core pyrrolidine ring structure.

Applicants respectfully traverse this rejection. As is set forth in Applicants' claims, including new independent Claim 18, the pyridine ring formed by the linkage of R^2 and R^3 is *substituted* (Claim 18 states that R^2 and R^3 are bonded together to form a substituted piperidyl). As set forth in the present specification, one or more hydrogen atoms bonded to *carbon atoms* in the ring are replaced with other substituents in a substituted heterocyclic group (*e.g.*, a substituted piperidyl). As such, in addition to the linkage to the $C(R^1)(R^1)_x$ moiety, or wherein x is 0 then the core ring structure A, the piperidine ring formed by R^2 and R^3 must be substituted with some other moiety at any of the carbon atoms of the ring. See specification at page 6, lines 10 – 14; page 8, lines 1 – 11; and page 9, lines 13 and 14. As set forth in the specification and as is also evident based on Applicants' claims, this requirement for a *substituted* heterocyclic ring structure formed by R^2 and R^3 is not optional but rather a required element of the present invention.

In contrast, the cited structure set forth in Sato fails to describe or suggest a substituted piperidine ring structure. As such, Applicants' claims are novel and patentable over Sato, and the rejection should be withdrawn.

CONCLUSION

Applicants therefore respectfully request that the Examiner allow Claims 2, 4, 5, 9, 11, and 18 – 31 as presented herein. If the Examiner believes that personal contact would be beneficial for disposition of the present application, she is respectfully requested to contact the undersigned at her earliest convenience.

Respectfully submitted,

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Registration No. 43,787
Telephone: 513-622-0159

March 19, 2002

Version with Markings to Show Changes Made

AMENDMENT TO THE SPECIFICATION

The title of the present specification has been amended as follows:

~~2-~~SUBSTITUTED ~~HETEROCYCLIC~~ PIPERIDINE AMIDES~~COMPOUNDS~~ AND METHODS OF THEIR USE

Page 4, paragraph 3 (lines 9 – 12) of the specification has been amended as follows:

"Heteroatom" means an atom ~~other than carbon~~selected from the group consisting of sulfur, phosphorous, nitrogen, and oxygen, e.g., in the ring of a heterocyclic group or the chain of a heterogeneous group. ~~Preferably, heteroatoms are selected from the group consisting of sulfur, phosphorous, nitrogen, and oxygen atoms.~~ Groups containing more than one heteroatom may contain different heteroatoms.

AMENDMENTS TO THE CLAIMS

Claims 1, 3, 6, 7, 8, 10, and 12 – 17 have been cancelled.

Claim 2 has been amended as follows:

2. The compound of ~~claim~~ Claim ~~1~~18, wherein A has 5 to 6 members.

Claim 4 has been amended as follows:

4. The compound of ~~claim~~ Claim ~~3~~2, wherein the substituted ~~heterocyclic group~~ piperidyl formed by R^2 and R^3 is substituted with a group selected from the group consisting of an aromatic group; a substituted aromatic group; a heteroaromatic group; a substituted heteroaromatic group; a substituted hydrocarbon group, wherein the substituted hydrocarbon group is substituted with a group selected from the group consisting of an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group; and a substituted heterogenous group, wherein the substituted heterogenous group is substituted with a group selected from the group consisting of an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group.

Claim 5 has been amended as follows:

5. The compound of ~~claim~~ Claim ~~1~~18, wherein R^4 is $-S(O)_2-$ and R^5 is $-O_rR^6$.

Claim 9 has been amended as follows:

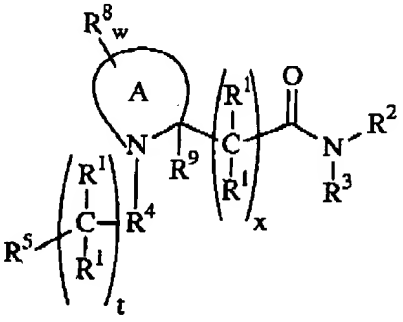
9. The compound of ~~claim~~Claim ~~1~~18, wherein R^4 is -C(O)-C(O)- and R^5 is $-O_rR^6$.

Claim 11 has been amended as follows:

11. The compound of ~~claim~~Claim ~~1~~4, wherein R^4 is $-CH(R^1)-$ and R^5 is $-O_rR^6$.

New Claim 18 has been added as follows:

18. A compound having the structure:



or an optical isomer, diastereomer, enantiomer, pharmaceutically-acceptable salt, biohydrolyzable amide, biohydrolyzable ester, or biohydrolyzable imide thereof, wherein:

(a) w is 0 to about 6, x is 0 to about 10, and t is 0 to about 6;

(b) A is a substituted heterocyclic group having about 4 to about 9 members;

(c) R^1 is selected from the group consisting of a hydrogen atom, a hydroxyl group, a hydrocarbon group, a substituted hydrocarbon group, a heterogeneous group, a substituted heterogeneous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group;

(d) R^2 and R^3 are bonded together to form a substituted piperidyl;

(e) R^4 is selected from the group consisting of $-S(O)_2-$, -C(O)-C(O)-, and $-CH(R^1)-$;

(f) R^5 is selected from the group consisting of $-NR^6(R^7)-$ and $-O_rR^6-$, wherein r is 0 or 1; with the proviso that wherein R^4 is $-CH(R^1)-$ and R^5 is $-O_rR^6-$ then r is 1;

(g) R^6 is selected from the group consisting of a hydrocarbon group, a substituted hydrocarbon group, a heterogeneous group, a substituted heterogeneous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group; and
R^7 is selected from the group consisting of a hydrogen atom and R^6;

(h) R^8 is selected from the group consisting of a hydrocarbon group, a substituted hydrocarbon group, a heterogeneous group, a substituted heterogeneous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group; and

(i) R^9 is selected from the group consisting of a hydrogen atom and a hydrocarbon group.

New Claim 19 has been added as follows:

19. The compound of Claim 11, wherein r is 1.

New Claim 20 has been added as follows:

20. The compound of Claim 19, wherein R^1 is selected from the group consisting of hydrogen atom and hydroxyl group.

New Claim 21 has been added as follows:

21. The compound of Claim 20, wherein t is from 0 to about 3 and at least one R^1 is hydroxy.

New Claim 22 has been added as follows:

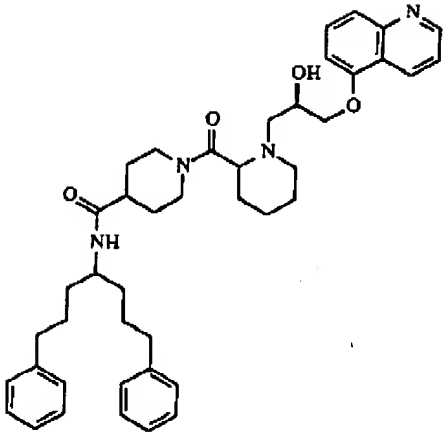
22. The compound of Claim 21, wherein x is 0.

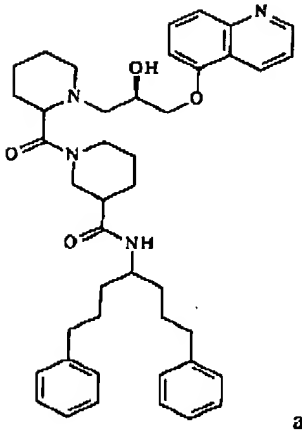
New Claim 23 has been added as follows:

23. The compound of Claim 22, wherein R^9 is hydrogen atom.

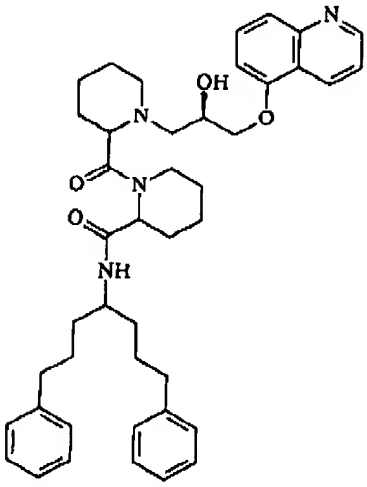
New Claim 24 has been added as follows:

24. The compound of Claim 23, having a structure selected from the group consisting of:





and



New Claim 25 has been added as follows:

25. A composition comprising:

(a) the compound according to Claim 18; and

(b) a pharmaceutically acceptable carrier.

New Claim 26 has been added as follows:

26. The composition according to Claim 25, wherein the compound inhibits transport protein activity.

New Claim 27 has been added as follows:

27. A composition comprising:

(a) the compound according to Claim 11; and

(b) a pharmaceutically acceptable carrier.

New Claim 28 has been added as follows:

28. A composition comprising:

(a) the compound according to Claim 24; and

(b) a pharmaceutically acceptable carrier.

New Claim 29 has been added as follows:

29. A method selected from the group consisting of treating multidrug resistance, inhibiting transport protein activity, and combinations thereof, comprising administering to a mammal in need of such treatment or inhibition the composition according to Claim 18.

New Claim 30 has been added as follows:

30. A method selected from the group consisting of treating multidrug resistance, inhibiting transport protein activity, and combinations thereof, comprising administering to a mammal in need of such treatment or inhibition the composition according to Claim 11.

New Claim 31 has been added as follows:

31. A method selected from the group consisting of treating multidrug resistance, inhibiting transport protein activity, and combinations thereof, comprising administering to a mammal in need of such treatment or inhibition the composition according to Claim 24.